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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/126,945	Applicant(s) Libermann et al.
	Examiner Scott D. Priebe, Ph.D.	Group Art Unit 1632

X Responsive to communication(s) filed on *Apr 5, 1999* .

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *11-16, 19, and 24-136* is/are pending in the application.

Of the above, claim(s) *11-16 and 19* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *24-26, 28, 29, 31, 32, 34, 35, 37-53, 55, 56, 58, 59, 61, 62, 64-84, 101* is/are rejected.

X Claim(s) *27, 30, 33, 36, 54, 57, 60, 63, 85-100, 110, and 112* is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

X The drawing(s) filed on *Jul 31, 1998* is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,6,9*

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

The amendments filed 4/5/99 and 12/9/99 have been entered. Claims 1-10, 17-18 and 20-23 have been cancelled. Claims 24-136 have been added. Claims 11-16, 19 and 24-136 are pending.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-10, 17 (second part) and 21 in Paper No. 8 filed 11/12/99 is acknowledged. The traversal is on the ground(s) that there would be no "serious burden" to search groups I and II, since the nucleic acid sequence would predict a protein sequence. This is not found persuasive because as set forth in the restriction requirement the subject matter of Groups I and II have acquired a separate status in the art as shown by their different classification; the search required for each group is not required for the other groups; and have acquired a separate status in the art because of their recognized divergent subject matter. While disclosure of a nucleic acid sequence might uncover a protein, other types of subject matter, not relating to nucleic acids, must be searched in determining the patentability of the proteins of Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-16 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8 filed 11/12/99.

Drawings

The drawings are objected to because Table 1, while transmitted as a drawing, has not been labeled as such and has not been referred to as a separate drawing in the 'Brief Description of the Drawings'. It is unclear whether applicants intend Table 1 to be a drawing or part of the specification. If the former, Table 1 should be labeled as a drawing or figure and a brief description thereof inserted into the "Brief Description of the Drawings". If the latter, Table 1 should be inserted into the specification, and the specification pages renumbered accordingly. Correction is required.

Claim Objections

Claims 128-136 are objected to because of the following informalities: Claim 128 is poorly written, and does not clearly reflect the description of this embodiment as disclosed on pages 19-23, for example, which states that "m" and "n" refer to N-terminal and C-terminal amino acid positions relative to positions in SEQ ID NO: 2. In claim 128, "the amino acid sequence m-n ... 15 to 335" should be re-written as --an amino acid sequence from position m to position n of SEQ ID NO: 2, wherein m is an integer from 2 to 321, n is an integer from 15 to 335, and m is less than n--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to polynucleotides encoding a polypeptide that is a fragment of SEQ ID NO: 2 (or by the corresponding clone) that regulates "epithelial gene expression", and methods and products for making such a polypeptide.

The specification as originally filed provides no clear support for fragments that regulate generic "epithelial gene expression". The specification discloses that PDEF regulates expression of the Prostate-specific Antigen (PSA) gene, and does not disclose any other genes or genera of genes regulated by PDEF. It further discloses that PDEF gene expression is highly specific, primarily to the prostate. The specification provides only an assay for determining function of a given PDEF polypeptide with respect to regulation of PSA gene expression. In addition, there is no evidence of record that any and all genes expressed in any and all types of epithelial cells share any common regulatory controls, or that regulation of the PSA gene shares any common regulatory features with any other genes expressed in epithelial cells. Thus, there is no evidence of

record that applicants were in possession, when the instant application was filed, of the invention that is now being claimed. These claims should be limited to fragments that regulate expression of the Prostate-specific Antigen gene.

Claims 24, 38-51, 64-83, and 121-127 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application contains a polynucleotide clone encoding PDEF, ATCC Deposit No. 203072, that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that clone is essential for practicing the claimed invention, being explicitly recited in the claims, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809. While the deposit was made under the terms of the Budapest Treaty, an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific clone has been deposited under the Budapest Treaty AND that the clone will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, must be filed in order to fully comply with all of the requirements of C.F.R. §§ 1.801 through 1.809.

Claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111, and 113-120 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a "nucleic acid" that encodes SEQ ID NO: 2 or a fragment of SEQ ID NO: 2 (as recited in the claims), does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO: 2 or a recited fragment of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111, and 113-120 are drawn to a polynucleotide that is either at least 90% (or 95%) identical to a polynucleotide that encodes all or a fragment of SEQ ID NO: 2. (It is presumed that the recited cloned DNA encodes SEQ ID NO: 2.). The claims appear to be directed to polynucleotides that encode proteins or polypeptides, and methods and products for making same, because of recitation of "SEQ ID NO: 2". All of the utilities for polynucleotides taught in the specification require that either the polynucleotide will hybridize with a PDEF nucleic acid or that it encode a polypeptide, either with PDEF function or that can be used to make antibodies that will be specific for a PDEF protein. The specification does not teach any use for a polynucleotide that cannot be used for these purposes.

Any two polynucleotides that encode a given amino acid sequence can be significantly less than 67% identical to each other if all possible wobble bases are different (depending on how

many amino acids that have codons with 2 wobble positions are present). This means that the sequences could differ by more than every third nucleotide. Relative to a specific polynucleotide, e.g. the open reading frame of SEQ ID NO: 1, the vast majority of polynucleotides that encode the same amino acid sequence would be closer to 65% identical than to 100% identical to the specific polynucleotide: as the sequence identity decreases, the number of polynucleotides increases geometrically. Polynucleotides which differ at every tenth nucleotide, let alone at every third, will not form stable heteroduplexes (Kennell, Prog. Nucl. Acid Res. Mol. Biol. 11: 259-301, 1971, see para. bridging pages 260-261), and certainly will not at the high stringency conditions required to hybridize to naturally-occurring polynucleotides that encode a given protein such as PDEF. Clearly, even if the claimed invention were limited to nucleic acid sequences encoding SEQ ID NO: 2, the vast majority could not be used in hybridization against any target disclosed in the specification, i.e., SEQ ID NO: 1. The specification does not identify any other target polynucleotides. Further claiming polynucleotides that are between 90% to 100% identical or encode polypeptides that are between 90% to 100% identical further increases the number of embodiments that are inoperative in hybridization against SEQ ID NO: 1. One skilled in the art would clearly be required to engage in undue experimentation to determine target DNAs for which the inoperative embodiments (relative to SEQ ID NO: 1) could be used.

One skilled in the art would be able to make and use the invention for producing recombinant polypeptides subsequently used for making antibodies against peptides that are part or all of the disclosed PDEF protein or other naturally-occurring allelic variants of PDEF encoded

by DNA encompassed by the claims, which would not be expected to differ substantially from SEQ ID NO: 2. However, the specification does not identify any other naturally occurring PDEF polypeptides, such as homologues from other mammals, whose sequence is within the window encompassed by the claims other than that set forth in SEQ ID NO: 2. As indicated in the specification (page 25, lines 6-9), linear epitopes can be as small as 8-10 amino acids, and identifies (page 25, lines 10-16) only 20 potential small epitopes in PDEF (SEQ ID NO: 2). It is not clear that an antibody that recognizes a peptide sequence differing in 10% or more of amino acids would bind to a PDEF polypeptide or peptide fragment, and not preferentially recognize a peptide sequence derived from another unrelated polypeptide present in a sample. It is unclear how one skilled in the art could predict which of all the possible variant amino acid sequences could be used to make a suitable antibody to the PDEF protein, and the specification provides no guidance on the matter. Nucleic acid sequences that are less than 100% identical to a polynucleotide that encodes SEQ ID NO: 2 are substantially more problematic in that sequence differences would not be limited to substitutions, but also to insertions or deletions. Most insertions or deletions would shift the reading frame, giving rise to polypeptides that share only fragmentary similarity to SEQ ID NO: 2 and would also comprise completely heterologous peptide sequence. It is not clear that antibodies raised against such a mixture of peptide sequences could be used with any reliable specificity.

The specification does not provide any guidance on what amino acid residues are necessary and sufficient for PDEF biological activity. Neither the specification nor the prior art

reveals proteins with any more than cursory amino acid sequence identity to PDEF other than Ets family proteins, which do not share more than general functional properties with PDEF. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions would be permissible in a PDEF polypeptide, that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. It is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the PDEF protein, that one cannot predict *a priori* variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would be required to identify the necessary nucleic acid sequence derivatives encoding a biologically active PDEF protein with an amino acid sequence differing from SEQ ID NO: 2 since the amino acid sequence of such polypeptides could not be predicted *a priori*.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only a single amino acid sequence, SEQ ID NO: 2, for a polypeptide having the necessary properties for the disclosed uses, i.e. encoding an active PDEF protein or a polypeptide that could be used to make antibodies against a PDEF polypeptide, and provides no guidance on predicting polypeptide variants of SEQ ID NO: 2 which would be suitable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43, 46, 48, 67, 70, 72, 73, 76, 79, 81, 82, 113, 116, 118, 119, 125, 127, 129, 132, 134 and 135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43, 67, 76, 113, 132 and 129 are indefinite for recitation of "heterologous polynucleotide"; claims 46, 48, 70, 72, 73, 81, 82, 116, 118, 119, 125, 127, 132, 134 and 135 are indefinite for recitation of "heterologous regulatory sequence". In the art, the term "heterologous" when applied to nucleic acids or polynucleotides has several distinct meanings; two nucleic acids simply have dissimilar nucleotide sequences or are from different sources (different organisms) or are from different genes (same organism). In all cases, the meaning is comparative between two nucleic acids or polynucleotides, and the claims do not clearly indicate which nucleic acids are "heterologous" or in which context they are "heterologous". For example, a promoter for the PDEF gene would be "heterologous" to the adjacent PDEF coding sequence since the sequences would be different but would <u>not</u> be "heterologous" since the PDEF promoter and coding sequence are from the same organism and are associated in the genome. In addition, "regulatory sequence" is indefinite since the claim does not provide the context of "regulatory": there is no indication of what is regulated, transcription, translation, replication, enzyme activity, etc. Also, there is no clear indication as to what the "heterologous regulatory

sequence" is "operably associated". The vector of claims 46, 48, 49, 70, 72, 73, 81, 82, 116, 118, 119, 125, 127, 132, 134 and 13[illegible] already an "isolated polynucleotide" comprising the "nucleic acid". Consider an embodiment where the "isolated polynucleotide" is a yeast artificial chromosome comprising the "nucleic acid". In this context, "operably associated" with the "isolated polynucleotide" is meaningless. These claims should recite that the "regulatory sequence" is "operably associated" with the "nucleic acid", rather than the "isolated polynucleotide".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It is noted that "nucleic acid encoding an amino acid sequence" is interpreted as being open, i.e. the nucleic acid may encode an amino acid sequence comprising the recited amino acid sequence. It is also noted that claim 78, as written, embraces any polynucleotide comprising a nucleic acid that encodes an amino acid sequence comprising at least one codon for an amino acid

from positions 15-321 of SEQ ID NO: 1. For example, if m and n both equal the same integer between 15 to 321.

Claims 84, 101-108, 111-118 and 120-136 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Acc. No. AA[illegible]204 (Ref. AT-8 filed 2/11/99).

GenBank Acc. No. AA[illegible]204 discloses a isolated polynucleotide, vector (having heterologous promoters operably linked to the insert) and cell where the polynucleotide (514 nucleotides in length) comprises a nucleic acid (nucleotides 5-181) that encodes amino acids 277-335 of SEQ ID NO: 2. The polynucleotide differs from nucleotides 1240-1753 of SEQ ID NO: 1 by only three nucleotides (at positions 1241, 1432 and 1440), i.e. the polynucleotide is 99.4% identical to nucleotides 1240-1753 of SEQ ID NO: 1.

Claims 84, 103 and 128-136 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Dev. Biol. 151: 176-191 (1992).

Chen et al. disclose an isolated polynucleotide that encodes the *Drosophila* ets-4 polypeptide (page 182, Fig. 2C). Amino acids 71-94 of ets-4 are identical to amino acids 294-317 of instant SEQ ID NO: 2. Chen et al. discloses vectors comprising the polynucleotide, where a heterologous promoter is operably linked to the insert, and cells comprising the vectors (page 178 through page 179, col. 1).

Double Patenting

Applicant is advised that should claims 27, 30, 33, and 36 be found allowable, claims 54, 57, 60 and 63 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Allowable Subject Matter

Claims 27, 30, 33, 36, 54, 57, 60, 63, 85-100, 110 and 112 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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